

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES**

**MINUTES OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES
COUNCIL**

May 12-13, 2010

The National Advisory Environmental Health Sciences Council convened its one hundred thirtieth regular meeting on May 12, 2010 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. Dr. Linda Birnbaum presided as Chair.

The meeting was open to the public on May 12, 2010 from 8:00 a.m. to 3:00 p.m. and on May 13, 2010 from 8:30 a.m. to 11:45 a.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on May 12, 2010 from 3:00 p.m. to 5:30 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Council Members Present

Stephen Baylin, MD
Chris Bradfield, PhD
Julia Brody, PhD
Hillary Carpenter, PhD
David Christiani, MD
Richard Finnell, PhD
Joseph Graziano, PhD
Andrea Hricko, MPH
Mary M. Lee, MD
Grace LeMasters, PhD
R. Stephen Lloyd, PhD
CPT Michael Macinski
Sem Phan, MD, PhD
Jerald Schnoor, PhD
Kevin Stephens, MD JD

NIEHS Staff Present

Kathy Ahlmark
Janice Allen, PhD
Beth Anderson
John Balbus, MD, MPH
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Linda Birnbaum, PhD, DABT, ATS
Wanda Boggs
John Bucher, PhD
Matthew S. Burr
Janet Cakir, PhD
Pamela B. Clark
Jennifer Collins
Helena Davis
Caroline Dilworth, PhD
Dorothy Duke
Sally Eckert-Tilotta, PhD
Barbara Gittleman
Kimberly Gray, PhD
Rachel Gross
Astrid Haugen
Jerrold Heindel, PhD
Heather Henry, PhD
Marc Hollander
Joseph "Chip" Hughes, MPH
Michael Humble, PhD
Laurie Johnson
Paul Jung, MD MPH
Ed Kang
Annette Kirshner, PhD
Steven Kleeberger, PhD
Robin Mackar
Carolyn Mason
J. Patrick Mastin, PhD
Elizabeth Maull, PhD
Rose Anne McGee
David Miller, Ph.D.
Sri Nadader, PhD
Retha Newbold
Sheila Newton, PhD
Terry Nesbitt, PhD

Heather Nicholas
Liam O'Fallon
Michelle Owens
Jerry Phelps
John Pritchard, PhD
Leslie Reinlib, PhD
Margarita Roque
Elizabeth Ruben
John E. Schelp
Daniel Shaughnessy, PhD
Carol Shreffler, PhD
William Stokes, PhD
William A. Suk, PhD
Cheryl Thompson
Claudia Thompson, PhD
Raymond Tice, PhD
Frederick Tyson, PhD
James R. Williams
Leroy Worth, PhD
Darryl Zeldin, MD

Director, National Institutes of Health

Francis Collins, MD, PhD

Members of the Public Present

Danielle Carlin, PhD, UNC/EPA
Gary L. Ellison, PhD, MPH, NCI
William Elwood, PhD, OBSSR
Ernie Hood (Scribe)
Pamela Schwingl, Social and Scientific Systems, Inc.

I. Call To Order and Opening Remarks

Dr. Linda Birnbaum, Director of NIEHS and NTP, welcomed attendees and called the meeting to order. She noted that Council members Dr. John Essigman, Stefani Hines, Dr. George Leikauf, Dr. Kenneth Ramos, Dr. Palmer Taylor, and Ndesu Obot Witherspoon were unable to attend this meeting. She welcomed new Council members, who would not be voting at this meeting: Andrea Hricko, Keck School of Medicine, Dr. Mary Lee, University of Massachusetts-Worcester, and Dr. Julie Brody, Silent Spring Institute. Dr. Birnbaum thanked the retiring Council members and presented those in attendance with certificates of appreciation: Dr. David Christiani, Dr. Kevin Stephens, and Dr. Joseph Graziano. She noted that Dr. Essigman and Ms. Hines were also retiring and that their certificates would be sent to them. She then asked all present in the room to introduce themselves, which they did.

II. Review of Confidentiality and Conflict of Interest

Dr. Mastin then reviewed the Conflict of Interest and Confidentiality procedures, which was previously provided to Council members in written form, and went over various other administrative matters.

III. Consideration of February 2010 Meeting Minutes

Approval of the February 2010 minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Mastin also noted the dates of the upcoming Council meetings for members to add to their calendars.

IV. Report of the Director, NIH

Dr. Birnbaum introduced Dr. Collins, who has served as Director of the National Institutes of Health since August 2009.

Dr. Collins began his remarks by noting that he had been at NIEHS the day prior to the Council meeting, spoke at an all-hands meeting, toured NIEHS facilities, and met with Dr. Birnbaum and her senior staff.

He identified what he felt were the five major opportunities for research at NIH, which involve virtually all of the NIH institutes and all diseases: 1.) to apply the newly emerging high-throughput approaches to achieve comprehensive understanding of the ways genes and environment interact to result in health or disease, 2.) to translate scientific findings even more aggressively and empower academic investigators to play a larger role in translation (including accelerated toxicology), 3.) to contribute evidence to facilitate decision-making related to health care reform, 4.) to focus on global health issues in infectious and non-infectious diseases, and perhaps most importantly, 5.) to ensure that researchers and the biomedical community are nurtured, re-invigorated, and empowered, without which the other four opportunities could not be achieved. He noted that these opportunities will be particularly challenging because NIH is facing a budgetary situation that is not terribly favorable over the next year or two.

Dr. Collins discussed the mission statement of the NIH, which alludes to the importance of the “pursuit of fundamental knowledge about the nature and behavior of living systems,” stressing how basic research provides the foundation for applied research that directly addresses health problems. He cited the Nobel Prizes recently awarded to several NIH grantees as a good examples of that concept. As another example of sound fundamental science, he mentioned Dr. Karen Adelman of the NIEHS Laboratory of Molecular Carcinogenesis, who is using high-throughput technologies to study gene regulation, and has discovered that certain sets of genes appear to be poised for expression even before the appropriate stimulus has occurred. He briefly described the

work of the NIH Genes, Environment and Health Initiative Exposure Biology Program, part of which is to develop new biomarkers and technologies to help document various influences upon gene-environmental interactions. As an example, he cited the work of Dr. Charles Rodes of Research Triangle International, who has developed improved personal sensors of aerosol exposures.

Dr. Collins then discussed the balance of the NIH mission statement, which describes “the application of that knowledge to extend health life and reduce the burdens of illness and disability.” He noted that longevity has steadily increased in the U.S. over the past twenty years, with much of that increase directly attributable to the application of scientific advances in prevention and interventions emerging from NIH research. Similarly, chronic disability among the elderly in the U.S. has steadily decreased- a trend also attributable to NIH advances. He noted that although these are dramatic trends, they take place over decades, making it difficult to communicate the high value of NIH work to the public.

Dr. Collins cited The Sister Study and the Tox21 project as excellent examples of applied research being conducted by NIEHS, and provided some details about the current activities of both programs.

He proceeded to update attendees on the status of ARRA (the American Recovery and Reinvestment Act of 2009) funding received by NIH. He described the \$10 billion funding as “quite a wild ride,” with a deluge of new research activity produced in a very short period of time and impressive innovation as a result of the thousands of new projects proposed and approved. He reported that \$6.3 billion of the funding has been obligated, and that virtually all of it has been committed, much of the balance being the second year of two-year grants. He estimated that 50,000 jobs would be created or retained during the two-year period of economic stimulus. He cited bisphenol A research totaling \$19.6 million and engineered nanomaterials research totaling \$11.9 million as significant examples of NIEHS ARRA-funded research projects.

Dr. Collins then discussed the need to maintain investment in innovation in the face of upcoming budgetary constraints. Discretionary funding from the NIH Common Fund is available to fund innovative programs that do not fit easily into any particular institute’s portfolio. This support includes programs such as Transformative RO1s, the NIH Director’s Pioneer Award, and the New Innovator Award. He also spoke of the importance of addressing the lack of diversity in the scientific workforce, citing the establishment of the NIH Director’s Pathfinder Awards, which will provide seven ARRA-funded awards totaling \$6 million to fund new approaches to improving scientific workforce diversity.

Looking at the trends for the NIH budget, Dr. Collins noted that after five years of a flat budget, in which NIH lost 16% of its buying power due to inflation, stimulus funding provided a big boost in FY2009 and FY2010. However, despite the addition of \$1 billion over the base from FY2010, the loss of ARRA funding in the FY2011 budget still represents a significant downturn in overall spending—"the cliff," as he characterized it. He said that NIH institutes will likely look favorably upon no-cost extensions for ARRA-funded programs that have been unable to spend their entire grants in the two-year time frame. In terms of congressional appropriations, he reported that the committees are under a great deal of budgetary pressure at this time, and that the community should be prepared for some challenges as a result over the next year or two. He showed a graph depicting NIH success rates over the past twenty years, which have steadily declined in recent years, describing the high degree of uncertainty about the trend for the near future. Although that uncertainty exists, he said it is almost impossible to see how the success rate would fail to fall below 20%, a historically low level.

Thus, Dr. Collins said, it is more important than ever to make the case for the value of scientific research at every opportunity. Communicating the benefits of the scientific enterprise and supporting educational efforts to inspire passion for science must continue and expand. For example, he noted that this day was National Lab Day, a nationwide effort to connect scientists and teachers, with scientists visiting classrooms and communicating directly with young people to get them excited about science. As part of the NIH outreach efforts, Dr. Collins noted the new brochure, "NIH: Turning Discovery into Health."

He then solicited questions from the audience.

Ms. Hricko asked Dr. Collins about NIH efforts to communicate directly to the public. He replied that NIH has many pathways for doing so, specifically noting the National Library of Medicine, which has the task of communicating the results of medical research to the public as part of its mission. NLM services, such as MedlinePlus, are heavily utilized by members of the public looking for information. He also mentioned regular workshops for members of the press, to provide them with background information and knowledge about pertinent topics in biomedicine. Noting the success of NASA in communicating with the public, he asked for suggestions to improve the performance of NIH in that area. Dr. Christiani mentioned that NIH grantees are often featured in television programs about science and medicine, but that the NIH connection is rarely, if ever, highlighted. He suggested the NIH Communications Department might be more proactive on that. Dr. Collins agreed that it was a common occurrence, with the university connection featured while the NIH connection is often not mentioned. He talked about his guest essays in *Parade* magazine as one vehicle for highlighting NIH achievements on a regular basis, and that other such opportunities should be sought.

Dr. Christiani asked whether the NIH budget outlook might be even worse than shown by Dr. Collins. Dr. Collins agreed that since much of the budget is taken up by salaries, the rest of the flexible budget may actually be losing ground.

Dr. Finnell asked Dr. Collins how, given the anticipated budgetary “cliff”, NIH would deal with the enormous opportunities presented by the completion of the knockout mouse program, now with the opportunity to phenotype extensively. Dr. Collins replied that the worst thing NIH could do is just hunker down and wait for the storm to pass, at the expense of much-needed innovative programs. He said that he had told the various interested Institute directors who had been funding the knockout mouse effort that if they would continue their funding for phenotyping, he would match their contributions from the Common Fund, basically doubling the amount available for the program. He added that it was going to be vitally important to continue to push forward with translational efforts, particularly drug development initiatives, as bold, innovative programs still need to be supported even in tough budgetary times. For example, the Cures Acceleration Network (CAN) program put forward by Senator Specter in the health care reform bill would authorize an additional half-billion dollars, and it’s through a marketable, translational strategy such as that that NIH may be able to do slightly better than the President’s current budget proposal.

Dr. Graziano asked Dr. Collins about his impression of the future direction of the Human Microbiome Project, which is supported by the Common Fund. Dr. Collins agreed that it is an exciting new opportunity to discover the spectrum of microbes present in the human microbiome in health and in disease. He felt that the idea that a “deranged” microbiome is present and perhaps contributing to diseases such as eczema and Crohn’s disease is promising, as is the exciting recent data suggesting that the microbiome is different in obese individuals and may contribute to that phenotype. He said it is the perfect example of a Common Fund project, and that it may well contribute to a new understanding of disease causation.

Dr. Stephens endorsed the idea of NIH enhancing its relationships with state and local health departments, noting that it could be quite mutually beneficial. Dr. Collins agreed, stating that in the past NIH had relied on CDC to maintain those contacts, but that it should be done as Dr. Stephens suggested, particularly since under the current administration such cross-agency cooperation and collaboration is being actively encouraged.

Dr. LeMasters said she wanted to see some bold initiatives on prevention. Dr. Collins replied that the third of his five initiatives, regarding the science of health care reform, actually involves a substantial amount of prevention, in order to help “change our sick care system to a health care system.” He mentioned reimbursement for preventive care as one important element, as well as the emergence of more individualized preventive

strategies. He added that it would be important to better understand health behaviors, particularly in light of the availability of genetic risk information, and to assess the impact of that data on prevention. He described a large, longitudinal, prospective study of 500,000 Americans that had been proposed six years ago but was never funded, and stated that he would still like to see that investigation funded.

Dr. Bradfield asked about the pursuit of the “expose-ome,” the idea of banking RNA and exploring transcriptional factors. Dr. Collins agreed that it will be important to investigate the epigenome and the transcriptome as reflections of expression. With high-throughput sequencing approaches now supporting such inquiries, protocols are being developed, and that type of investigation will be expanding tremendously in the near future, he said. Other aspects of epigenetics are progressing rapidly as well, such as methylation studies, he added. He noted, however, that the technology in proteomics has not developed as rapidly as he had hoped. He also alluded to another Common Fund project, the Genotype-Tissue Expression (GTEx) project, as an ambitious effort to characterize the transcriptome, taking a snapshot in 160 deceased human donors of how genetic variation, gene expression and epigenomics are connected. Dr. Birnbaum added mention of the Roadmap Epigenomics program, of which NIEHS is one of the co-leads. Dr. Baylin elaborated about the “mosaicism” of the target tissue when discussing environmental impacts on the epigenome, stating that isolation of the cell types would be necessary for such studies. Dr. Collins speculated that perhaps IPS cells may have value in such investigations, being isolated and then exposed to various environmental insults. Dr. Birnbaum added that one of the experiments in the Epigenome program is to look at the methylome of 160 different cell types.

Dr. Lloyd commented that there seems to be a perception within study sections that make it difficult to achieve funding for high technology utilization in innovative projects, since many are perceived to be “fishing expeditions.” Dr. Collins recognized the culture clash between gatekeepers who prefer hypothesis-driven projects and the divergent goals of large-scale, discovery-driven projects. He felt that it may be a healthy debate, but that there are ample reasons to consider discovery science over the last ten years to have been “incredibly fruitful.”

Mary Gant asked Dr. Collins whether environmental factors would be explored within the Microbiome Project. He replied that the groundwork was being laid by the Common Fund project in hopes that individual institutes would then explore areas of interest to them in relation to the microbiome—so, he said, “Go forth.”

Dr. Birnbaum thanked Dr. Collins for his remarks.

V. Report of the Director, NIEHS

Dr. Birnbaum began her presentation by updating Council on NIEHS involvement in responses to the Gulf of Mexico oil spill. Chip Hughes, Director of the Worker Education and Training Program (WETP), and his staff have been participating at the Federal Command Center in Louisiana, and have been evaluating training and safety protections put in place for cleanup workers. WETP has developed an online resource to assist training efforts, and staff and grantees are updating Emergency Support Activation Plans to be ready for deployment.

Dr. Birnbaum also updated Council on NIEHS participation in federal initiatives on climate change and health, particularly citing the April 22 release of a white paper report, *A Human Health Perspective on Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change*. John Balbus, NIEHS Senior Advisor for Public Health, is co-chairing the Trans-NIH Working Group on Climate Change and Human Health. Dr. Birnbaum also highlighted the role of NIEHS in several other federal-level initiatives regarding climate change.

Dr. Birnbaum briefly summarized NIEHS budget projections for FY2010 and FY2011, noting that the 2011 increase would only be 2.6%, versus the overall 3.2% increase for NIH as a whole. Superfund, however, will see a 3.2% increase. She reported that searches are underway and progressing for the currently open top NIEHS leadership positions, including Scientific Director, Deputy Director, and DERT Director, all of which are currently filled by acting officials. She mentioned that Dr. Aubrey Miller was recently added to the NIEHS Bethesda office, and that recruitment is currently underway for a toxicology liaison, who will also work in the Bethesda office. She noted that adding staff to the Bethesda office will allow NIEHS representatives to attend Bethesda/Washington meetings that are often called with little or no notice.

Dr. Birnbaum updated Council on some of the notable recent scientific publications by NIEHS staff or grantees. First, she highlighted a paper in *Science* by Dr. Karen Adelman's intramural group, describing promoter-proximal stalling and arrest of pol II in *Drosophila*, a finding with major implications for understanding the mechanisms of gene transcription. The second paper she described, published in *PLoS One* by NIEHS grantees, contains the first definitive epidemiologic evidence supporting the concept of chronic vascular response to exposure to particulate matter in adults. Among other findings, atherosclerosis was found to progress twice as fast in people living within 100 meters of a major highway in California. She reported on a publication in the *Journal of Allergy and Clinical Immunology* emerging from an ongoing collaboration between NIEHS intramural and extramural scientists, which described genome-wide association studies to identify candidate genes associated with childhood asthma susceptibility in a Mexican population.

Dr. Birnbaum told Council about a recent article by the intramural Epidemiology Branch, published in *Environmental Health Perspectives*. The paper, a product of the ongoing Sister Study, reported that greater risk of early fibroid diagnosis was associated with soy formula during infancy, maternal pre-pregnancy diabetes, low childhood socioeconomic status, and gestational age at birth. Another notable paper, from *ACS Nano*, described a cytotoxicity assay used to evaluate nanoparticle toxicity and to help design safer nanoparticles. She then reported on a publication in *Thorax* from the Southern California Children's Health Study, which examined the role of inducible nitric oxide synthase in asthma risk and lung function during adolescence. The investigators found that DNA sequence variation in the promoter region of *NOS2A* plays a potentially important role in respiratory health and development.

Another intramural-extramural collaboration, with the intramural Microarray group, produced the next publication (in *Hepatology*) described by Dr. Birnbaum. The researchers examined changes in human peripheral blood gene expression in response to a dose of acetaminophen that did not induce detectable levels of liver injury. The findings may aid in efforts to identify better biomarkers of drug-induced liver injury. Finally, Dr. Birnbaum mentioned a paper from the National Toxicology Program reporting on experiments in which mice were chronically exposed to a dioxin-like compound found as a contaminant in some herbicides. The animals developed urethral carcinomas, an extremely rare neoplasm. The findings serve as a model for cancer of the urinary tract as well as aiding understanding of mechanisms of dioxin-like compounds in carcinogenesis.

Dr. Birnbaum continued by reporting on recent institute highlights, including two recent opportunities for her to testify before Congressional subcommittees, as well as Congressional staff briefings and a Senate breakfast meeting. She also mentioned an NIEHS-NTP seminar on Environmental Exposures and Women's Health, held March 2, 2010 at Bethesda, and recent activities on the NTP Draft Brief on Soy Infant Formula, which underwent peer review at the NTP Board of Scientific Counselors (BSC) meeting on May 10, 2010. The BSC will meet June 21-22, 2010, to peer review draft substance profiles for the 12th Report on Carcinogens. She noted recent honors received by NIEHS scientists Richard Paules, Trevor Archer, and Gwen Collman. Recent important meetings described by Dr. Birnbaum included the inaugural Partnerships for Environmental Public Health Meeting and a major NIEHS presence at the Society of Toxicology annual meeting in March at Salt Lake City. That meeting brought several NIEHS scientists and grantees awards and distinctions, and featured over 30 talks and 60 poster presentations from NIEHS/NTP personnel. She also reported on several high-level meetings she has had recently with officials from the FDA, NIOSH, the CDC, NTSDR, and other agencies.

Dr. Birnbaum concluded her presentation with a brief update on some of the NIH Common Fund Projects with NIEHS participation, several of which had been described by Dr. Collins. She then asked for questions from the Council.

Dr. Christiani asked whether there had been any progress on the establishment of an environmental health sciences study section at NIH. Dr. Birnbaum replied that discussions are still ongoing between NIEHS and the NIH Center for Scientific Review (CSR). CSR is ensuring that NIEHS grants are not being orphaned in the process, and that all study sections include participants who are familiar with NIEHS and its work. She said that those are the current developments, and that NIEHS is optimistic that they will help its grantees.

VI. OppNet 101: An Introduction to NIH's Basic Behavioral and Social Science Opportunity Network

Next, Dr. Claudia Thompson of NIEHS and Dr. William Elwood of the NIH Office of Behavioral and Social Sciences Research (OBSSR) introduced Council to a relatively new trans-NIH initiative for basic behavioral and social science research called OppNet.

The concept of interaction between behavioral and social sciences factors and health has been around for quite some time, said Dr. Thompson, having been codified in 1995 with the establishment of the OBSSR within the NIH Director's office. OppNet is designed: 1.) to pursue shared opportunities that strengthen basic Behavioral and Social Science Research (b-BSSR), 2.) to foster relevant activities and initiatives on basic social processes and mechanisms of behavior, and 3.) to expand NIH's funding of b-BSSR. Dr. Thompson depicted the organizational structure of OppNet, which includes a significant role for NIEHS, including Dr. Birnbaum's membership on the program's Steering Committee. Dr. Annette Kirshner is the NIEHS representative on the OppNet Coordinating Committee.

Dr. Thompson described the role of NIEHS in b-BSSR as the study of the impact of environmental factors (e.g., noise, climate, environmental hazards) on behavioral and social function, and the interplay of environment, behaviors, and health.

OppNet Facilitator Dr. Elwood then spoke, describing a bit more of the historical context for OppNet, as well as outlining the operational definition of b-BSSR and elaborating on that definition in the context of environmental health sciences (e.g., cognitive processes of tenants as they receive information about lead, asbestos or mold abatement projects). He presented the three categories of b-BSSR: 1.) understanding human or animal functioning to improve understanding of the mechanisms of behavioral and social processes, 2.) biopsychosocial research, and 3.) development of methodology and measurement to support research in the first two categories.

Dr. Elwood described the results of an all-day OppNet retreat held April 19, 2010, which built upon an extensive planning process that had led to the founding of OppNet in 2009. Early in 2010, a web-based RFI was issued, soliciting input regarding challenges, opportunities, and measures of success for OppNet. The more than 350 responses were then analyzed and narrowed down to themes and concepts for the retreat. On May 4, 2010, the top 7 FOA ideas were presented to the Steering Committee. By July 2010, OppNet will issue FY2011 FOAs.

Dr. Elwood reported on the funding for OppNet, which is co-funded and co-managed by a consortium of 24 Institutes and Centers (ICs) and 5 program offices within NIH. He said that in FY2010, OppNet receives \$12 million, of which \$10 million is ARRA funds, with \$2 million for HIV/AIDS-related research projects. From FY2011-FY2014, OppNet will be partially funded by a fixed percentage of each IC's base appropriation. In FY2011, this will comprise \$10 million, with another \$10 million coming from the NIH Director, for a total of \$20 million. For FY2012-FY2014, the total budget will rise to \$30 million annually.

Dr. Elwood described the FY2010 FOAs that Council would be seeing at its summer meeting. One is for mentored career development in b-BSSR for mid-career and senior investigators; the rest are competitive revisions to existing ARRA initiatives.

Dr. Elwood concluded by showing a screen shot of the new OppNet home page, <http://oppnet.nih.gov> He then opened the floor for questions.

Dr. LeMasters asked about the inclusion of "genes and environment" as one of the concepts presented as parts of OppNet. Dr. Thompson explained that it was seen as one of the environmental factors intertwined with behavioral responses to impact health. Dr. Elwood mentioned that understanding the cognitive processes involved in decision-making in light of personal genetic information is a fertile field for OppNet study in the future, as is the role of culture in effectively conveying health information. Dr. LeMasters asked why nutrition and diet was missing from the list of factors. Dr. Thompson replied that it was only appropriate to consider diet and nutrition in the context of other environmental exposures. NIEHS would be interested in diet as a contributor to environmental factor in overall health; OppNet would be more interested in how people process particular dietary information to make decisions affecting their health.

Ms. Hricko asked whether policy decisions would play a role in the OppNet initiative, in terms of how public officials absorb information and behave as a result, with the data influencing their policy decisions. Dr. Elwood replied that that particular pursuit would largely depend on the PIs and their applications to OppNet.

VII. Concept Clearance #1: Human Health Impacts of Climate Change

Dr. Mastin introduced DERT Program Administrator Dr. Caroline Dilworth, who presented to Council the first concept clearance on a new research program called Human Health Impacts of Climate Change (HHICC). Rather than a concept for a single RFA or set of RFAs, HHICC is designed to be a multi-year program to include not only funding initiatives, but also a means for coordinating relevant research within NIEHS, collaborations across NIH and other governmental agencies, and other activities to foster new research in this important environmental public health area.

According to Dr. Dilworth, most of the climate-related research to date has concentrated on atmospheric science and climate forecasting, with less research specifically focused on the potential human health impacts of climate change. Aside from the direct effects of temperature rise, climate change will also result in environmental changes such as sea level rise, changes in precipitation patterns, degraded air quality and increased exposure to pollutants, all of which could affect human health. Mitigation and adaptation strategies could also have consequences for human health, either positive or negative. She commented that HHICC is inherently a multi-disciplinary endeavor; thus identifying opportunities for collaborations will be crucial for success.

Dr. Dilworth briefly reviewed the white paper on this topic recently issued by NIEHS, which had been presented earlier in the meeting by Dr. Birnbaum, as an illustration of increased federal agency activity and attention to the issue of HHICC. She noted that several of the eleven human health and disease categories addressed in the white paper are already high-priority areas of interest for NIEHS, as are many of the environmental pathways thought to lead to those downstream health effects, and several of the cross-cutting issues identified in the report.

Dr. Dilworth noted that the December 2009 Trans-NIH Workshop on Climate Change and Health had identified five major research gaps, which have formed the building blocks for the proposed NIEHS HHICC initiative:

- Health impacts of climate change and weather variability
- Health impacts of mitigation and adaptation strategies
- Assessment and characterizations of population vulnerability to climate change
- Methods and models development
- Risk communication and education

Dr. Dilworth said that those building blocks will organize the program's activities designed to meet the HHICC goals: 1.) To provide a structure to coordinate and support research and related activities to better understand how climate change will directly and indirectly affect human health risks, and 2.) To coordinate research within NIEHS,

across the NIH, and with other federal agencies. Key activities to help achieve those goals will include: 1.) Leveraging ongoing research programs and capacities, 2.) Promoting submission and funding of unsolicited grants in relevant areas, 3.) Providing specific research funding opportunities, and 4.) Identifying opportunities for multidisciplinary/interagency collaboration.

Dr. Dilworth then provided more detail on each of the five research area building blocks, with examples of potential projects within each area.

She identified several short-term goals for moving forward with the program should it be approved. Immediate activities would include integration of climate-specific language into ongoing initiatives, beginning to work with the NIH Center for Scientific Review, and continuing trans-NIH and federal coordination efforts. She also said that based on available funds, she would anticipate that FOAs would be released annually under the HHICC program, including both Program Announcements and Requests for Applications. Also, efforts to release collaborative FOAs with other NIH ICs and sister federal agencies will be a priority for the program. She illustrated the types of funding initiatives anticipated by describing a proposed FY2011 Program Announcement—an NIH Program Announcement with Special Review, with multiple ICs participating, focusing on assessing population vulnerability to climate change.

Dr. Dilworth concluded her presentation by summarizing the key points she had discussed, and then asked for comments from the designated Council reviewers.

Dr. Carpenter said that the proposal would help to fill a major data gap currently being faced by state departments of health, including his in Minnesota. He felt it would help public health agencies take the next step forward in the way they are able to address climate change issues. He had one suggestion, urging the institute to get a quick start on the epidemiology effort.

Dr. Graziano said he was “enormously supportive” of the initiative, and glad to see NIEHS take a leadership role.

Dr. Christiani asked whether the initiative would involve intramural as well as extramural research. Dr. Dilworth replied that at present it would be mainly an extramural process, but that intramural involvement across several ICs would be desirable. Dr. Christiani said he would encourage intramural involvement, particularly given NIEHS toxicological expertise. Dr. Pritchard said NIEHS would actively move to bring NIEHS intramural resources to bear on this initiative.

Dr. Schnoor also expressed his support for the program. He asked Dr. Dilworth to elaborate on the priorities laid out, particularly regarding indoor air quality issues with relation to flooding events. She answered that the white paper had specifically not

attempted to set any priorities on the research areas identified, but that indoor air would certainly be included. Dr. Balbus agreed that climate change and respiratory health is a high priority for the institute, adding that he has been asked to speak at an American Thoracic Society workshop on the issue, and to a new NRC committee on climate change and indoor air, so it is a very timely topic of considerable interest to the institute. He added that it should be pointed out that this overall topic is very much tied to global health as well, and that the federal government's global climate change research program is transitioning from a focus on climate science to an agenda responding to and acting upon climate change itself. As such, he said, the federal government is looking to the health sector to lead the way in showing how to apply basic science in the real world. So there is a tremendous expectation for NIEHS to show leadership in this area, he noted, as well as a very strong interest and support at the highest levels of HHS.

Dr. Graziano agreed that prioritization will be a critical step going forward with the project.

Dr. Birnbaum noted how rapidly NIEHS had entered this very important area, and mentioned that it may be necessary to institute a special study section to accommodate funding.

Approval of the concept was moved and seconded, and Council voted unanimously in favor.

VIII. Concept Clearance #2: Validation and Field Testing of New Tools for Characterizing the Personal Environment and Biological Response Indicators

Dr. David Balshaw began his presentation of the concept clearance by acknowledging the contributions of his co-leads, Dr. Daniel Shaughnessy and Dr. Kimberly Gray, from the Susceptibility and Population Health Branch, as well as the involvement of many colleagues from the Exposure Biology Program (EBP). The goal of that program is to link personal exposures to biology to disease. This concept is designed to address major gaps in environmental epidemiology by supporting the development of personalized environmental sensors to characterize external contacts (e.g. chemical exposures, diet and lifestyle, psychosocial stress, and drug abuse), and the development of biomarkers and biosensors to document biological responses to exposures (e.g. oxidative stress, inflammation, DNA repair/damage).

Citing substantial progress in the development of new tools in both areas, Dr. Balshaw said that the goal now is to apply the tools in population-based studies. To that end, EBP personnel have been working to engage the end users of the new devices, by participating in scientific sessions at numerous societies, focused discussions, and

demonstrations of the technology. Feedback from those activities has shown that although the end users are excited about the technology, they will require adequate sensitivity, specificity and reproducibility, willingness by study participants to use the devices, robust performance in the field, added scientific value, and affordability.

Regarding the readiness of the technology, Dr. Balshaw reported that generally the tools are past the initial concept/proof of principle phase, and have moved into testing and validation in a controlled environment. The progression is similar in biomarker validation, as candidate biomarkers are moving into the pre-validation and validation phases.

Dr. Balshaw explained that this concept proposed a focused demonstration effort encompassing a two-year RO1 encouraging partnerships between the developers of the tools and the end users. Those partnerships would be designed to support validation and improvement of the devices and expanded field study, not parent development of the tools. For both candidate biomarkers and prototype sensors, a variety of metrics characterizing their validity, usability, and value will be employed.

Dr. Balshaw noted that although his presentation appeared to be heavily focused on GEI, the proposed program is not restricted to GEI activities, nor is it focused exclusively on NIEHS activities. There are verbal commitments to participate from several ICs, and the expectation that several more will eventually sign on.

Next, the reviewers gave their opinions on the proposed program. Dr. LeMasters disclosed that she was involved in one of the sensor development projects, and reported that it had been an interesting experience for health people to be working with engineers. She felt there had been great progress in all of the sensor projects, and that they and the biomarker development projects are currently at a critical stage, with the need now for the new systems to be able to assure reliability and validity. She pointed out that end users would comprise more than just researchers; that worker training and hazmat groups would be likely to use the technology on a large scale as well. She expressed strong support for the proposed two-year program.

Captain Macinski felt it was important to get the new tools out of the laboratory and into the field to ensure that they actually work, and that it was even valuable to discover what fails and devote no further resources to those failures, concentrating on more promising projects.

Dr. Graziano asked Dr. Balshaw to enumerate which devices were at this phase of development. He replied that within the 8 GEI projects, there were 3 groups looking at particulate matter at the 3 major levels, 3 sensors looking at volatiles, including organics, toxic industrial chemicals, and molecular gases, one sensor focused on pesticides, and one on allergens.

Dr. Lee said she felt that this program was “a vital link.” She asked Dr. Balshaw to comment on how the connections would be made between biomarker developers and investigators. He replied that that had been part of the early considerations with the program, in an effort to connect with early users who would have large numbers of samples available for analysis. Dr. Shaughnessy elaborated that there is an Opportunity Fund in GEI designed to help conduct some early validation studies with epidemiologists. Activity has included contact with an investigator at NCI who has a large store of banked samples from studies in China, testing biomarkers for validity in stored samples of high exposures. There has also been informal contact with several NIEHS-supported investigators about their willingness to be contacted later for access to samples for biomarker validation. Several indicated their willingness to eventually participate in such studies.

Dr. Mastin requested and received a motion and second to approve the proposal, and Council voted unanimously to do so.

IX. Concept Clearance #3: Dietary Influence on the Human Health Effects of Environmental Exposures

The meeting’s third concept clearance was presented by Dr. Kimberly Gray of the Susceptibility Population Health Branch. She began with a summary of the major points in the presentation, beginning with providing Council working definitions of *diet* and *nutrition*. She then described a model for the modification by diet of our response to environmental exposures. Diet can have either a negative or a protective effect when combined with exposures to environmental toxicants. In the negative scenario, diet can exacerbate the onset of inflammation or oxidative stress (or another pathway), leading to environmental disease.

The objectives of the proposed program are:

- To invigorate and support a body of science to explore potential links between dietary factors and environmental exposure leading to disease, and
- To better understand the mechanisms underlying these complex interactions to enable the development of effective primary prevention and intervention strategies to mitigate environmentally-induced diseases.

Dr. Gray outlined the history of NIEHS interests in the interplay of diet and environment, which is a concept that has permeated several past research funding opportunities in fetal basis of adult disease, oxidative stress studies, epigenetics, and more, and has been included in several past workshops and meetings, including the 2006 Comorbidity of Environmentally Induced Disease workshop and the 2009 meeting of the International Society of Environmental Epidemiology held in Dublin. These events

demonstrated global interests in the influence of diet and nutrition to modulate the effects of environmental exposures on human health, jettisoning the proposed program.

Dr. Gray described trends in US diets since the 1970s, with, for example, increased consumption of soft drinks and other foods sweetened with corn derivatives as opposed to cane sugar. The dietary trends have been attributed to the epidemic rise in overweight, obesity and extreme obesity in the US since the mid-70s, with today more than 72% of Americans defined as overweight or obese. Further complicating the issue, the diet-toxicant disease paradigm stems from various pathways and affects different subpopulations in different ways.

Dr. Gray proceeded to relate some examples from the recent literature of what is currently understood about the impacts of diet and nutrition on environmentally-induced diseases. She cited a recent study suggesting that the Mediterranean diet has a protective effect on respiratory health, particularly asthma, allergy, and allergic rhinitis incidence and severity. She then described a recent study which showed that exposure to TCDD, a dioxin like compound used as flame-proofing agent and as a pesticide against insects and wooddestroying fungi, and diet can impact the estrogen pathway, with early life exposure to TCDD and a high fat diet interacting to increase breast cancer risk by changing metabolism capacity. She reported on another study in mice that suggested a potential association between the consumption of prenatal supplements, including folate, vitamin B12 and zinc, and the appearance of asthma in children (and possibly grandchildren, implying an epigenetic effect), a result that still needs to be confirmed in human studies.

After reviewing the program's objectives, Dr. Gray described the need for a multi-phased approach, including targeted research opportunities to support small-scale exploratory human and basic science projects, support of conferences and workshops in the area to bring researchers of disparate backgrounds and disciplines together to help identify data gaps, and collaboration with sister federal agencies to identify new scientific opportunities related to the issue and leverage some of their existing resources.

She then noted several suggested topics for the initiative to explore, including both applied and basic research projects. Applied project suggestions included the expansion of existing studies looking at the interplay of diet, environmental exposures, and health outcomes, studies to develop new methods and tools to measure diet and environmental exposures, and development of new analytical methods or models to incorporate multiple layers of data presented by measures of diet and environment. Basic projects could include identification of dietary pathways, use of well-established animal models of environmental disease to investigate the impact of diet, and the

identification of key molecular pathways that may be potentially useful in prevention and intervention.

Future plans envisioned for the Dietary Influence on the Human Health Effects of Environmental Exposures program include the creation of a firm research base to develop prevention/intervention strategies, and expansion of the scope of work by NIEHS to support future large-scale projects designed to explore a wide range of exposures, dietary scenarios, and disease endpoints in applied and basic research. Program staff will work closely with other interested ICs to develop workshops to identify research gaps, to host and present research results at relevant national or local conferences, and when appropriate to work at the local level to disseminate knowledge and generate interest. Evaluation will be another key component, with the development of metrics to assess and evaluate outcomes connected with the program.

Dr. Gray then introduced the designated discussants for the concept clearance, Drs. Finnell and LeMasters. Dr. Finnell expressed great support for the proposal, citing the fact that there are significant data gaps with respect to nutrition and environmental health. He said he views the project as “not another epigenetics exercise.” His only hesitation was the impression that the proposed project was taking “baby steps,” where the community feels that an all-out research effort should be launched in this area, including partnering with existing programs. Dr. LeMasters said that she sees the concept as being “very cross-cutting” in issues, particularly in an ability to work on studies of the impact of nutrition in children and in hormonal effects in girls, such as breast development and obesity. She characterized the proposal as an environmental justice issue also, particularly in cities where concentrations of metals such as lead dust, high air pollution levels, and perhaps poor nutrition by residents may contribute cumulatively to adverse health outcomes. The inner cities, she said, would be good areas to focus on with prevention strategies. She also cited the need for more studies of male hormonal issues such as fertility. Overall, she felt that the proposed concept is long overdue and should be integrated into the institute’s overall research strategy.

Dr. Stephens suggested using grocery stores’ bonus card data as a rich source of valuable information regarding food and beverage consumption, perhaps even correlating with prescription drug usage.

Dr. Lloyd suggested that the project should include examination of the role of the microbiome in obesity, citing recent animal data supporting the hypothesis that the microbiome contributes to obesity.

Dr. Christiani said he felt that since diet can be so broadly defined, it might not be appropriate for NIEHS to spearhead the effort being proposed; that it should be a major undertaking with significant participation by several of the other NIH ICs. He

recommended a narrower focus for the program, concentrating on the impact of contaminants in the food supply, such as pesticides. Dr. Gray responded by emphasizing that there must be an environmental toxicant involved in any research proposal for NIEHS to provide funding, and that in partnerships with ICs such as NHLBI and NCI, those agencies could study main effects not involving environmental toxicants, but at the same time they have expressed strong interest in the role of environmental elements such as indoor air.

Ms. Hricko asked Dr. Gray to comment on plans to study the question of limited access to quality foods (grocery stores, non-fast food restaurants, etc.) in the inner city as it impacts the health of minority group populations. Dr. Gray responded with several examples of existing research on that issue, including projects by NCI and NHLBI. She said that within the context of the proposed project, there would be a role for the development of prevention and intervention strategies and communication materials.

Dr. LeMasters asked whether the current cohort studies of pubescent girls at breast cancer centers include the gathering of dietary intake data. Dr. Dilworth replied that such information is in fact being collected at all three sites (Mt. Sinai, California, and Cincinnati). Dr. Gray mentioned similar work being done at several of the children's centers. Dr. LeMasters said that it sounds like there's been a good start in looking at exposure/nutrition interactions in girls, but again recommended that similar questions be looked at in boys. Dr. Gray noted a current study in Russia that is doing so, although it is in its early stages.

Dr. Stephens recommended that the cost of food also be included as an important variable to be considered in the proposed research.

Dr. Mastin then asked for and received a motion and second that the proposed concept be approved, and Council voted unanimously in favor of the proposal.

X. Report of the Office of Communications

Dr. Birnbaum introduced Ms. Christine Flowers, NIEHS/NTP Director of Communications, who reported to Council on recent activities and developments in the Office of Communications and Public Liaison (OCPL).

Ms. Flowers has been in her present position for six years, and has revamped the institute's communications program in that time. Initially, she said, efforts were concentrated on streamlining the institute's branding and visual identity, and strengthening media relations. Today the office also publishes the monthly newsletter *Environmental Factor*, administers the NIEHS website, helps with study recruitment, coordinates ceremonies and protocol needs, responds to public inquiries, works on national science conference exhibits and poster sessions, community forums, and

facility tours, provides training on media, writing and presentation skills, prepares speeches, talking points and PowerPoint presentations, participates in new media and social networking, responds to Freedom of Information Act (FOIA) inquiries, and coordinates internal communications within the institute.

In 2004, NIEHS was virtually unknown among national media reporters, with only 25 citations in news stories. By concentrating on building relationships with media personnel and communicating proactively with the press, today NIEHS is far better-known as an important source of valuable information in environmental health sciences—in 2009, the institute was cited in 4,855 news stories, responded to more than 1,000 media requests, and arranged 130 media interviews for NIEHS scientists.

Bisphenol A generated considerable national coverage, including NIEHS scientists appearing on *The Today Show* and *NewsHour with Jim Lehrer*, and stories in publications such as *Time*, *People*, *Nature*, and the *Milwaukee Journal Sentinel*. Dr. Birnbaum was featured in stories on endocrine disruptors in *USA Today*, *Frontline*, and *Scientific American*, as well as an article on the funding of research in *Nature*. Other NIEHS personnel and research have been profiled in *Newsweek*, *National Geographic*, *Second Opinion*, North Carolina Public Television, *Our State*, the NIH's *Medline Plus* publication, and many more. Telephonic press conferences have been used to increase access, and in November, 2009, OCPL staged a transatlantic press conference on climate change, a satellite simulcast from the National Press Club in Washington and the London School of Hygiene and Tropical Medicine, which generated more than 385 news stories.

Although many other NIH ICs do not quantify their news coverage, NIEHS compares well given the office's much smaller relative budget and staff resources, including citations in the NIH's daily e-clips service.

Ms. Flowers reported that there has also been considerable progress with the institute's online newsletter, *Environmental Factor*. With increased coverage of institute events and a proactive distribution plan, there was a 60% increase in visits in 2009. 2010 has seen the addition of a "share" feature and video and other multimedia to the publication, which promise to increase interest even further.

The NIEHS website was completely revamped recently. The homepage is now updated daily, and educational materials such as brochures and fact sheets are available on the homepage as well for easy access by visitors. The website logged 8 million page views in 2009.

OCPL has also produced materials to assist with successful recruitment efforts for 33 separate studies and programs, including the Sister Study and the Environmental Polymorphisms Registry.

Ms. Flowers described various media training programs, and event programming such as the successful grand opening of the NIEHS Clinical Research Center in July, 2009.

The 2010 Society of Toxicology meeting in Salt Lake City afforded OCPL an opportunity to expand its social networking efforts by providing live updates from the meeting, including live tweets. The *Live at SOT* website received 6,000 visits over the course of the five-day meeting.

Moving forward, OCPL will concentrate its efforts on web-based communications, as that is increasingly where Americans are turning for their news, and for information about the federal government. Social media participation is progressing at NIH institutes, although slowly, as there are inherent challenges. One area for NIEHS has been the addition of a “share” function with every *Environmental Factor* story, by which a reader can send the article to social media outlets such as Facebook and Twitter, or email it to colleagues and friends.

OCPL also wants to encourage all NIEHS/NTP personnel to think of themselves as ambassadors for the institute, as part of the collective communications effort. Part of that effort will be for OCPL to equip the ambassadors with the appropriate tools to help communicate effectively and positively about the institute and the science, including palm cards with brief talking points, a redesign of the employee website, and email notifications about new fact sheets and brochures as they are released. OCPL also plans to strengthen its partnerships, including an expanded version of the *Live at SOT* program for the 2011 meeting, where it will be a highlighted feature of the conference, along with work with SOT to develop posters and promotional materials focused on the group’s 50th anniversary.

Ms. Flowers concluded by thanking her team, and opened the floor for questions.

Dr. Mastin recognized the outstanding work done by OCPL as ARRA awards were being prepared.

Dr. Christiani inquired about the possibility of an NIEHS jingle. Ms. Flowers mentioned the NIEHS slogan, “Your Environment Is Your Health,” which has been shortened to “Your Environment, Your Health.” She commented that it is important that any such branding element refer back to people’s frame of reference, such as relating to people that NIEHS is the group that told them about the health hazards of lead, mercury, and asbestos. Dr. LeMasters felt that there is limited information available about the savings, in terms of dollars, health, and lives, brought about by the environmental health sciences, so she suggested that NIEHS focus on the impact that findings from research have had or could have on public health or health care costs. Ms. Flowers replied that her office is always on the lookout for success stories, and that right now cost savings are one important area of interest. She pointed out that one challenge faced by NIEHS

is that its successes often are the results of lifestyle changes, such as preventative measures, as opposed to the more readily communicated benefits of a new pill or cure.

Dr. Brody asked Ms. Flowers to comment on the role of investigators themselves, with their focus on the unknown in their research. Ms. Flowers agreed that that is a challenge, and that her office never wants to overstate the science, being very careful to focus on the key finding of the particular research—what makes it important, and why people should care about it. She said that her staff works closely with the investigators to craft accurate messages that are true to the science while clearly communicating the important public health implications in a manner designed to attract attention from the public.

Dr. Lloyd asked whether OCPL does a better job on capturing intramural or extramural research, or whether they carry equal weight, and recommendations on how to solve any disparity between the two. Ms. Flowers felt that both organizations get equal attention, with much communication emanating from the intramural program and NTP, and with close coordination with grantees on communication efforts.

Dr. Schnoor asked how OCPL determines what news they will communicate. Ms. Flowers replied that her group works closely with internal scientists, and checks in regularly with grantees to keep abreast of their developments. She mentioned that press releases are not the only way to communicate new developments; there are also emails, newsletter articles, and other vehicles. Dr. Schnoor asked who decides what is newsworthy. Ms. Flowers replied that it is a team effort involving all of the top officials at the institute working in ongoing coordination with her office. Dr. Birnbaum added that OCPL is extremely responsive to tips from leadership on items of potential news interest for follow-up.

XI. Consideration of Grant Applications

This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

XII. Concept Clearance #4: Small Business Innovation Research (SBIR) Contract Studies

Dr. Kleeberger called day two of the meeting (May 13, 2010) to order. Following announcements by Dr. Mastin, Dr. Shaughnessy presented the next concept clearance regarding topics for SBIR to Council. He began with a brief review of the basic structure of the SBIR program, noting that NIEHS is required to set aside 2.5% of its grant budget for SBIR grants, and 0.3% for the Small Business Technology Transfer (STTR) program. He also reviewed the three stages of the SBIR/STTR process: feasibility, full

research/R&D, and commercialization, noting that NIH typically does not support the Phase III commercialization efforts.

NIEHS currently funds \$10.9 million in SBIR grants, \$1.3 million in STTR grants, and \$1.33 million in SBIR contracts. Each year, suggestions for contracts to develop new technologies or products are solicited from NIEHS scientists. These topics are presented to Council for review and approval. Then, in August, they become part of an NIH Omnibus SBIR Contract Solicitation. Contract offers are received in early November and reviewed in early Spring by a special emphasis panel assembled by the NIEHS Scientific Review Branch.

Five topics are proposed this year, all from the NTP.

Topic 1: Application of “Omics” Technologies to Rodent Formalin-Fixed, Paraffin Embedded Tissue Samples (Dr. Raymond Tice)

Topic 2: High Throughput Screening for Reactive Oxygen Species Mediating Toxicity (Dr. Raymond Tice)

Topic 3: In Vitro 3D Tissue Models for Toxicity Testing (Dr. Raymond Tice)

Topic 4: Development of Improved Biomarkers as Earlier Humane Endpoints for Ocular Safety Assessments (Dr. William S. Stokes)

Topic 5: Development of Sensitive Innovative Methods for Detecting and Assessing Pain and Distress in Laboratory Animals Used in Toxicological Research and Testing (Dr. William S. Stokes)

Dr. Shaughnessy provided details on each of the topics, and then asked the designated discussants for their comments. Dr. Bradfield felt that all five topics looked promising, but felt that the first might be limited in terms of potential commercialization. On the first topic, he expressed concern that with the ongoing emergence of new technologies, the NTP tissue sample archive might be exhausted at some point. Dr. Bucher said that NTP is very sensitive to that issue, and has a committee that reviews requests for access to samples.

Dr. Phan said that he was in general agreement with these topics, particularly #1, and is very supportive of the program itself. He was more hesitant about Topic 3 on development of 3-D tissue culture models, citing the complexity of toxicological responses, which go beyond just tissue damage to include immunological and inflammatory factors. Dr. Shaughnessy said that those factors were in fact in the process of being worked into the models to enhance their relevance to in vivo toxicity.

Dr. Lloyd inquired about the increase in funding caps that Dr. Shaughnessy had mentioned. Dr. Shaughnessy clarified the fact that Phase 2 is now \$1 million *per year*, and confirmed for Dr. Lloyd that the “fast track” Phase 1&2 program is continuing.

Dr. Mastin asked for and received a motion and second for approval of the concept. Council voted unanimously in favor of the concept.

XIII. Concept Clearance #5: DERT-NTP Collaborative Research Program

According to presenter Dr. Heindel, the overall goal of the proposed program is to provide funding mechanisms for ongoing interactions between NTP and DERT-funded scientists. There would be a variety of mechanisms designed to ensure long-term commitments. Involvement of NIEHS-funded investigators in NTP studies would allow the NTP to expand the scope of their research by taking advantage of methods in use in the grantees’ laboratories, and would in turn provide new opportunities for academic investigators themselves.

This is not an entirely new concept, said Dr. Heindel. In 1997, 1998, and 1999, R03 RFAs were issued for DERT-NTP funding collaborations. In each of those years, six grants were funded.

The initial proposed collaborative study is a Bisphenol A (BPA) Chronic Rat Study. NIEHS is currently the major US funding agency for BPA studies, including 12 new grants with ARRA funds to fill data gaps and FDA concerns about the validity and repeatability of investigator-initiated studies. This research plan has been developed by NIEHS, NTP, and FDA to better understand BPA toxicity by conducting studies of pharmacokinetics, behavior, and chronic toxicity after perinatal exposures. It is intended to provide information that is most useful to regulatory agencies for human risk assessment of BPA-containing products. The study design, by NTP/FDA, will be GLP-compliant, utilizing chronic lifetime exposures starting during development and lasting throughout the course of life, long enough to detect and assess long-term disease outcomes. Additional endpoints will be proposed and carried out by DERT-funded investigators. As part of that process, DERT will develop an RFA to solicit the scientific expertise of the academic investigators, asking for details on their proposed additional endpoints, rationale for including those endpoints in the study, their background and expertise in the field, and how the proposed endpoints could be included in the study design. Those proposals will be subject to NIEHS Scientific Review, and if the science appears solid, the next step would be an internal technical feasibility review. A consortium of investigators with specific expertise will be funded, who will work with FDA/NIEHS/NTP scientists to incorporate the selected endpoints into the final study design.

Results of the study are expected to:

- Strengthen the database on dose-response for toxicological effects of BPA.
- Strengthen the interaction between NTP-FDA and the scientific community.
- Establish new linkages between regulatory and investigative science to enhance the risk assessment process for endocrine-active substances.

The FOA will be issued in June, 2010, using a U01 mechanism, with funding of 5-7 consortium grantees to be awarded in February/March 2011. The in-life portion of the study will start in June 2011 and end in June 2013, after which time data analysis and integration will take place, along with publications emerging from the study.

In the future, a BPA mouse chronic study is under discussion, and other NTP-initiated interactions and collaborations are envisioned using a variety of funding mechanisms. Success of the BPA rat study will provide a model for future collaborations looking at endpoints associated with exposures to other chemicals.

Dr. Heindel concluded his presentation and asked the reviewers for their comments. Dr. Schnoor said he felt that the study would be a win-win for DERT and NTP, with the added benefit of the FDA-compliant design. His only concern was effective communication among the extramural researchers as a group, and with the NTP. Dr. Heindel agreed that that was an important point, and assured Dr. Schnoor that such communication would occur. Dr. Finnell said he was generally favorable to the concept, but was curious to see whether the collaborative model would work as envisioned. He also wondered what the ultimate metric of success would be, and whether that would include increased FDA attention to investigator-initiated studies in this area. Dr. Heindel replied that showcasing to the FDA the value of the addition of the investigator-led endpoints to the GLP-backed study was a secondary goal of the project. Dr. Bucher added that one fascinating part of the intersection between academic and regulatory research is the concept of adversity, with the regulators looking for solid evidence of adversity in toxicological studies, while academic investigators tend to focus their endpoints on *potential* for adversity. He said that BPA was an important model in that respect for the many endocrine-active agents that will be studied in the near future, and noted that BPA may go away commercially before the scientific studies are completed, but that it would still be fruitful to continue the investigation. Dr. Heindel added that this study will use more doses than the typical study, and then the data will be analyzed to see whether the top doses would have detected all adverse effects, with the intent to help regulatory agencies determine whether this assay does or does not pick up the activity of endocrine-disrupting chemicals.

After some discussion of the reasons for the choice of the rat as the animal model, Dr. Bradfield asked how the U01 mechanism would work. Dr. Heindel replied that NIEHS would fund 6-8 U01 grants each of which would assess a specific endpoint of the NTP/FDA BPA study and together they would form a consortium that would work

together to assure that all the endpoints were integrated into the larger study and that the data analysis was coordinated across all studies.

Dr. Carpenter asked whether non-classic estrogenic effects of BPA, which appear to be involved in its toxic mechanism, will be considered in the study. Dr. Heindel answered that a wide variety of endpoints would be studied, including non-estrogenic ones such as metabolic syndrome and immune responses.

Dr. Mastin asked for and received a motion and second for approval of the concept. Council voted unanimously in favor of the concept.

XIV. Concept Clearance #6: NIEHS-NSF Oceans and Human Health Initiative

Dr. Frederick Tyson presented this concept to Council. He began by briefly reviewing the history of the existing NIEHS-NSF Centers for Oceans and Human Health (COHH), four centers initially funded in 2004. This collaboration has created the unique scientific discipline known as Oceans and Human Health (OHH). The goal of the COHH program was to promote interdisciplinary collaborations between biomedical and ocean scientists to improve knowledge of the impact of the oceans on human health, focusing on harmful algal blooms (HABs), water- and vector-borne diseases, and marine-derived biopharmaceuticals and probes. In terms of scientific publications and leveraged funding, the program has been quite successful. New techniques have been developed and applied by the centers, including genomic detection of toxins and organisms in seafood, sea water and sea air, and use of biosensors to attempt to predict HABs formation. Food safety has become an area of particular concern for the centers, as they have explored human and animal exposures and the health effects of toxins. One good example of the program's impact on public health was the 2005 HAB in New England—by being able to predict the bloom thanks to recent discoveries, area residents were prevented from consuming contaminated shellfish.

The need for further exploration of oceans and human health is clear, with 60% of the world's population living near coastal areas, and 53% of the US population living in coastal counties, a number expected to rise to 75% by 2025. These trends are inexorably increasing the use of coastal and marine resources. Aside from exposure to naturally-occurring pathogens such as HABs, there are many sources of man-made contamination as well, including pesticides, pharmaceuticals, and other potentially harmful materials.

The proposed new collaboration with NSF will include marine issues such as HABs and anthropogenic pollution, as well as a concentration of research resources on the Great Lakes, including geophysical and anthropogenic impacts on/contributions to the development of micro-organisms producing cyanotoxins in the largest freshwater supply in the world. Global climate change will also be incorporated into the initiative as it

impacts oceans. The program will also include investigation of marine-based natural products—pharmaceuticals and bioactive molecules. However, this aspect of the program will be solely supported by the NSF.

The new initiative, according to Dr. Tyson, will include both a center program (P01 mechanism) and single projects (R01 mechanism). The centers will focus on HABs, marine pollution, modeling, and global climate change. Single projects will include marine HABs, Great Lakes human health research, and marine natural products. Annual funding will be \$6 million, with NSF contributing \$4 million and NIEHS committing \$2 million. Review will be conducted at NIEHS by Dr. Linda Bass. Dr. Tyson expects funding to cover 3-4 center awards and 2-4 R01 awards, with two separate RFAs to be released in mid- to late June, with awards ultimately being made in May, 2011 (These dates will be pushed back 1-2 months due to Dr. Tyson's health). Management will be joint, including grantee meetings, center director calls, and other mechanisms for interactions.

Dr. Tyson then asked for comments from the concept's reviewers.

Dr. Graziano called the program "a real wow." He compared it with the Superfund in that it has integrated disciplines effectively with innovative collaborations. He said he was impressed with the program's productivity, particularly given the relatively modest NIEHS investment. Dr. Carpenter agreed, calling it "an amazing program." He was especially thrilled with the inclusion of the Great Lakes and climate change.

Dr. Lloyd recommended that if there are outstanding applications that may exceed the budgetary parameters, there should be consideration to increasing funding, given the importance of the issues involved. Dr. Tyson agreed.

After brief further discussion, Dr. Mastin asked for and received a motion and second for approval of the concept. Council voted unanimously in favor of the concept.

XV. Scientific Presentation: Xenobiotic Efflux Pump Expression, Function and Regulation at the Blood-Brain Barrier

Dr. Pritchard introduced NIEHS intramural research Dr. David Miller, Chief of the Laboratory of Toxicology and Pharmacology. One of the main areas of focus in his laboratory is transporters, which are the major determinants of where xenobiotics will go in the body by uptake, tissue distribution, and excretion. The same transporters handle therapeutic drugs, and there are interactions between delivery of environmental toxicants and therapeutic drugs. Transporters are the critical determinants of xenobiotic toxicity and drug efficacy, thus protecting against toxic effects while limiting drug therapy. Better understanding of how transporter activity and expression are regulated

should lead to improvements in limiting neurotoxicity and efficacy of CNS drug therapy. It is known that these characteristics are altered in disease states.

Although the blood-brain barrier (BBB) is an extensive network of capillaries up to 4 miles in total length, the capillary endothelium only comprises less than 1% of brain volume.

Dr. Miller's team focuses largely on the BBB efflux transporter P-glycoprotein (P-gp), because it handles a wide variety of therapeutic drugs and is highly expressed in the brain capillaries. It is also seen a quite potent, as suggested in an experiment with knockout mice in which the pharmacodynamics of methadone were profoundly affected (nearly a full order of magnitude) by the deletion of P-gp. Other experiments involving increases in P-gp expression in the BBB resulted in dramatically reduced methadone efficacy.

Inhibiting P-gp in the BBB could allow improved brain access for chemotherapy drugs to treat brain tumors (although thus far this strategy has proven unsuccessful in drug company efforts). On the other hand, the protective effect of P-gp allows a drug like ivermectin to be highly effective against river blindness, since it does not pass the BBB but is highly toxic to the parasite that causes the disease.

Dr. Miller described a variety of methods used to assess ABC transporter activity and expression, including imaging techniques, specific assays, fluorescent probes, and *in vivo* measurements, several of which were developed in his laboratory. His team has characterized several signaling pathways affecting P-gp expression, including one with potential clinical implications in combating drug resistance in epilepsy. They have also identified signaling pathways that down-regulate P-gp *activity*—rapidly, transiently, and without change in P-gp expression. Thus they represent opportunities for changing the delivery of drugs to the brain. Other results have shown that exposing capillaries to β -amyloid reduces P-gp activity and eventually changes expression as well.

One experimental focus in Dr. Miller's lab has been to explore whether the aryl hydrocarbon receptor (AhR) is a link between environmental toxicants and altered CNS drug delivery, by using exposures to the dioxin TCDD. In *in vitro* experiments exposing brain capillaries to TCDD, P-gp activity is substantially increased, even at very low doses. That increase in activity is blocked by AhR antagonists. In a rat model, TCDD also dose-dependently increased P-gp expression and transport activity. To characterize the effect on transporter activity, *in situ* brain perfusion was used, and allowed the researchers to quantify the effects of various treatments in terms of their pharmacokinetic and pharmacodynamics effects, which were profoundly impacted by P-gp expression. This work has resulted in a new paradigm for environmental toxicants

that are AhR ligands—disrupted delivery of CNS drugs, depending on the type of P-gp substrate being used.

The second project described by Dr. Miller involves Alzheimer's disease (AD), which involves a harmful accumulation of β -amyloid proteins in the brain. The hypothesis is that BBB P-gp normally clears β -amyloid from the brain, and that P-gp-mediated transport is defective in AD. In one experiment, it was shown that P-gp transports a fluorescent β -amyloid-42 derivative. In a mouse model of AD, P-gp transport activity was discovered to be reduced in brain capillaries. This was early in the animals' life span, prior to the development of cognitive impairment, but with the initial underlying mechanisms related to AD, such as β -amyloid accumulation in the brain, at work. In the mouse model, there was a more than 50% reduction in specific transport of β -amyloid. The experimental questions then became: Can P-gp expression be restored in these mice? And will increased transporter activity lead to reduced brain β -amyloid levels? By dosing the animals with a PXR ligand, PCN, P-gp expression was restored, with levels reverting to those of the wild type animals. Also, markedly reduced β -amyloid levels were seen in the treated animals, both in brain capillaries and in whole brain homogenate. These significant results lead to two more important questions for future research: Can long-term P-gp induction (oral dosing) reduce brain β -amyloid levels, angiopathy, neurodegeneration, and cognitive impairment in the model animals, slowing the progression of the disease? And, how does β -amyloid signaling change in P-gp expression? That is a more basic question, while the first question has direct clinical implications as a direction for AD research and the development of therapeutics.

Concluding his presentation, Dr. Miller then opened the floor for questions.

Dr. Baylin asked about the role of transporters in embryonic development. Dr. Miller replied that the transporters all appear to be involved in multiple drug resistance in tumor cells. In terms of the relationship between the development of the BBB and neurotoxicity, very little is known at this point, he said.

Dr. Birnbaum asked whether Dr. Miller had any information about the relative dose-response curves for induction of P-gp in different tissues. He said that had been studied, but in a very crude way initially, and that it is a good question for future inquiry.

Dr. Lloyd asked about whether the expression or activity of P-gp appears to be affected in disease states such as metabolic syndrome, involving atherosclerotic plaque formation. Dr. Miller said that the data are sparse on that for the BBB, but that there is some contradictory data available for Type 1 or Type 2 diabetes. He felt that that field needs more definitive studies.

Dr. Graziano asked about the mechanistic understanding of the impact of lead poisoning on the BBB. Dr. Miller mentioned that there is some data on metals impact,

but in cell culture only. He said he would like to see similar experiments done in animal models, as well as animal studies of metal transport across the BBB. He said there were still many questions to be answered in this area in order to achieve mechanistic or molecular understanding.

XVI. Update on the Gulf Oil Spill—BP Gulf Oil Spill Response: Protecting the Responders

Dr. Birnbaum introduced Joseph “Chip” Hughes, Director of the Worker Education and Training Program (WETP), who gave the meeting’s final presentation, an update on the Gulf oil spill and the NIEHS response.

Mr. Hughes briefly related the history and mission of the WETP, which was established in 1986 to provide training and education to workers engaged in activities related to hazardous waste, hazardous materials transportation, and emergency response in both areas.

He showed Council a NOAA map forecasting the trajectory of the oil spill, which at the time had just begun to make significant contacts with land masses. With southeast winds prevailing, the plume was expected to continue to flow northeast toward Louisiana.

NIEHS has partnered with NIOSH and OSHA in responding to the immediate and future worker safety training and education needs related to the oil spill. Institute personnel are also working with BP officials to assess the exposures its responding workers may encounter, their personal protection needs, and strategies for training. NIEHS has deployed staff, subject matter experts and awardees for instructor training and worker protection outreach.

Mr. Hughes showed a slide depicting the progression in an emergency situation, ranging from *Rescue* to *Recovery* to *Cleanup*. He said the oil spill was then in the initial Rescue phase, which is inherently chaotic, with substantial risk-taking—a dangerous time when workers are often put into situations for which they are not adequately prepared. He stressed that BP is in charge of the emergency response and clean-up, which makes it necessary for non-BP personnel to put aside their personal feelings and work together with BP as effectively as possible. He said that it is proving challenging to graft a new model of federal response onto working with a private company that is a responsible party in the situation, particularly on this scale.

NIEHS training activation has taken place through the Worker Safety and Health Annex of the National Response Plan. NIEHS has been working with OSHA night and day since the spill to gather the most up-to-date scientific and health information, and has put it into a booklet for responders. That information is also readily available at the

NIEHS website. The booklets are being distributed to the staging areas of the Gulf Coast, providing the most pertinent information available for responders on the ground or on the water. They will be passed out by NIEHS and BP trainers at training classes, which are being conducted around the clock. The key health and safety messages in the training tool are:

- Proper training is a key component of a safe response and cleanup.
- The oil and hazardous materials associated with the cleanup can be hazardous to human health.
- The hazards and issues covered in this training tool are dynamic and require vigilance and flexibility.
- The key to a safe response is attention to the safety issues of your work environment.

Mr. Hughes said that it is important to institute procedures using the *hierarchy of controls* in the oil spill cleanup, rather than being in a situation in which individuals are acting and relying on personal protective equipment for their safety.

The booklet also contains a primer on oil spill cleanup, including information on booms and standard hazard communications materials, such as information on Material Safety Data Sheets. Mr. Hughes said that the major pending questions about the materials involved are the nature of the weathered crude oil, and the character of exposure risks related to the chemical dispersants being used and air exposures from burning of the spilled oil.

The booklet informs workers about the main potential routes of exposure, including skin contact, inhalation, ingestion, and injection. Skin contact is of particular concern in exposures to weathered crude oil, as is irritation due to inhalation of vapors.

NIEHS is also participating in an effort to assess research concerns related to exposure to crude oil, as this situation provides opportunities to advance knowledge. One specific concern is the difficulty of medical surveillance and human health exposure assessments related to the spill due to the size of the spill area and affected shoreline, as well as the large number of responding workers. A registry system has been established for workers who have received training through the BP training process, and all workers will have to go through the training process put in place by NIEHS and BP. They will be issued cards which will authorize access to the spill's "hot zones." Data will then be gathered from all workers who come into contact with the weathered crude. It remains to be determined whether basic or population-based research to investigate the long-term health effects related to exposures in this incident will be performed. Significant federal resources will need to be brought to bear, and it can be anticipated that NIEHS will be a significant part of that effort, he said.

He closed by remembering those workers who had died in the incident, and hoping that current efforts could prevent any more deaths among workers who have responded to the emergency.

Dr. Stephens asked about provisions regarding the mental health of the responders, noting that shrimpers and fisherman in the Gulf area had faced many challenges in that area after Hurricane Katrina, in which they lost so much. He also expressed concern about exposures to VOCs resulting from burning the oil, saying that his office in New Orleans had received many calls complaining about the smell of burning oil and respiratory irritation. Lastly, he wondered about the long-term effects on food, health, air and water after five years or more.

Mr. Hughes replied that he was very concerned about the lack of a system to work on the mental health needs of the responders, or the affected communities. Dr. Stephens related some of the problems faced by his staff people following Katrina, including two suicides, in hopes of ensuring that this aspect would be under consideration in the current situation.

Dr. Lloyd asked whether BP had made available samples of crude from the affected site for analyses regarding sulfur, heavy metal, and VOCs content, in order to establish baselines for comparison to subsequent samples taken from organisms in the food chain. Mr. Hughes replied that sampling was being conducted by contractors to BP, and that EPA, ORD and ERT are also involved. He mentioned that if there were any teams among the attendees who would be interested in becoming involved in that process, his office could facilitate the appropriate contacts to put that into motion.

Dr. Lloyd also expressed concern about UV exposures among responders, particularly in terms of UV-induced immunosuppression. He also wondered whether there could be a synergistic effect with dermal exposures to PAHs in terms of irritations or carcinogenesis. He asked whether there was an education effort in place regarding the immunosuppression effects of UV exposures. Mr. Hughes replied that there was not as yet such a program, and that it would mainly be a NIOSH issue. He said that it had been recommended to BP that it establish a scientific advisory group to be able to access the best science and scientists in environmental health science, and that perhaps NIEHS could have a role in that effort.

Ms. Hricko asked which NIEHS-funded university is providing the training for workers, and about the length of the course, whether it is only 4 hours, as being reported regarding BP, or the 40 hours recommended by NIEHS and OSHA. Mr. Hughes said that the exemption issued in 1989 during the Exxon-Valdez incident, allowing just 4 hours of HAZWOPER (Hazardous Waste Operations and Emergency Response) training, was in fact still in effect.

Captain Macinski asked whether EPA has been sampling the air at burn sites. Mr. Hughes recommended the EPA site, www.airnow.gov, noting that particulate matter monitoring data is publicly available on that site and is frequently updated.

Dr. Bradfield asked if researchers were taking serum from workers, whether IRB approval was necessary, and generally how exposures, which are currently at their highest levels, were being monitored. Mr. Hughes said that was not yet being done, but that work was going on to assess how to implement a medical surveillance program. He said that he felt a pilot group should be established from which to capture body fluids to begin exposure assessments. Dr. Bradfield felt that NIEHS should have a standing study section to conduct investigations in such situations. Dr. Birnbaum asked if NIOSH or CDC had such a program to be able to collect samples in an emergency situation. Mr. Hughes was unaware of such a program. Dr. Birnbaum said perhaps NIEHS should consider establishing such an initiative, because waiting a month or two after the crisis to take samples means the key time has been missed. She pointed out the difference between workers' exposures and exposures in populations in communities, which would take much longer, and that it would be critical to assess the workers' exposures through biological samples or questionnaires on a rapid response basis, although as human data the appropriate ethical controls would also need to be in place. Dr. Bradfield wondered whether it might be possible to have standing IRB approval in place for such situations. Mr. Hughes thought that was a good idea, but that the fact that it would be non-pre-surveilled, non-baseline population would present challenges to the basic science of the medical surveillance effort.

Ms. Hricko related her experience with the EPA stance on dispersants related to the 9/11 incident, in that there was an inconsistent message at the time. She asked Mr. Hughes what message was coming out regarding dispersants in this situation. He replied that it is important for the message to be consistent and solidly based on the science, not public relations concerns. He felt that the precautionary principle should be in force, in that public health risks related to these exposures have not been characterized.

Captain Macinski commented that it seems that health and safety standards are waived at very times when they are most needed. Mr. Hughes agreed.

Dr. Schnoor mentioned that the EPA air quality websites cited by Mr. Hughes were only based on coastline samples, and asked whether samples were being taken on the vessels in the spill area itself. Mr. Hughes replied that he believed such data did exist, but was not yet publicly available.

Dr. Birnbaum thanked Mr. Hughes for his presentation, thanked Council for a productive meeting, and then officially adjourned the NAEHS Council meeting.